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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/770,639	02/02/2004	Francisco Sanchez-Madrid	27331-501CIP2A	1583

30623 7590 02/05/2007

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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/770,639	SANCHEZ-MADRID ET AL.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-108* is/are pending in the application.

4a) Of the above claim(s) *1-55,61-66 and 70-104* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-60,67-69 and 105-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election, without traverse, filed November 6, 2006, is acknowledged.

   Claims 1-108 are pending.

   Applicant's election, without traverse, of Group X, drawn to a method of treating an unwanted immune response comprising administering a depleting anti-CD69 antibody, wherein the species of unwanted immune response is "rheumatoid arthritis", in the reply filed on November 6, 2006 is acknowledged.

   Claims 56-60, 67-69 and 105-108 are under examination as they read a method of treating an unwanted immune response comprising administering a **depleting anti-CD69 antibody**, wherein the species of unwanted immune response is **"rheumatoid arthritis"**.

   Claims 1-55, 61-66 and 70-104 have been withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being directed to non-elected inventions.

2. An Information Disclosure Statements does not appear to have been filed.

3. Acknowledgment is made of applicant's claim for foreign priority based on applications filed in **Spain** on **January 31, 2003 and November 5, 2003**. It is noted, however, that applicant has not filed a certified copy of these foreign applications as required by 35 U.S.C. 119(b).

4. The disclosure is objected to because of the following informalities: the first sentence of the instant specification reads as follows: "This application is a continuation-in-part of ES200302587, filed on November 5, 2003, which is a continuation-in-part of ES200300252, filed January 31,2003, each of which is incorporated herein by reference in its entirety."

   It is improper to indicate that the instant application is a "continuation-in-part" of ES200302587 or to indicate that ES200302587 is a "continuation-in-part" of ES200300252 because foreign applications are not U.S. Patent applications.

   Applicant is invited to strike "continuation-in-part" from the first sentence and rephrase it so that it is clear the instant application simply claims the benefit of priority of ES200302587 and ES200302587.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

   Each letter of trademarked terms should be capitalized wherever it appears and each trademarked term should be accompanied by the generic terminology, e.g., ™ or ®. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

   The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, for example the title should refer to CD69.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

   > The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. **Claims 56-60, 67-69 and 105-108 are rejected under 35 U.S.C. 112, second paragraph,** as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

   Claims 58-60 recite a method comprising administering a "depleting anti-CD69 antibody".

   It is noted that while the other claims under examination generically recite "early activation molecule depletor" or "CD69 depletor" be administered, ***as stated in the Restriction Requirement of October 11, 2006***, these claims have been ***restricted to the extent that they read on the administration of a "depleting anti-CD69 antibody" and will be examined as such, irregardless of the format of the claims.***

   Therefore, claims 56, 57, 67-69 and 105-108 are also included in the instant rejection.

   It is further noted that according to the instant specification, "[a]s used herein, 'CD69', ***also known as 'very early activation' protein, 'activation inducer molecule', and 'gp 34/28'***, refers to ***mammalian CD69***, preferably human CD69 protein." (see instant specification page 45).

   The instant claims are indefinite in the recitation of "depleting anti-CD69 antibody" as the sole means of identifying these antibodies because **"CD69"** is merely a laboratory designation and the term **"CD69"** does not clearly define this antibody in that artisans could use the same designation to define a completely distinct biological material, or in the

alternative, could use a different designation to define the exact same antibody, like "anti-gp 34/28".'

Applicant is invited to claim the antibody with reference to the particular sequence that it recognizes, e.g., "wherein said depletor is a depleting antibody that binds SEQ ID NO: 2".

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. **Claims 56-60, 67-69 and 105-108 are rejected under 35 U.S.C. 112, first paragraph,** as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 58-60 recite a method comprising administering a "depleting anti-CD69 antibody".

It is noted that while the other claims under examination generically recite "early activation molecule depletor" or "CD69 depletor" be administered, ***as stated in the Restriction Requirement of October 11, 2006***, these claims have been ***restricted to the extent that they read on the administration of a "depleting anti-CD69 antibody" and will be examined as such, irregardless of the format of the claims.***

Therefore, claims 56, 57, 67-69 and 105-108 are also included in the instant rejection.

It is further noted that according to the instant specification, "[a]s used herein, 'CD69'...refers to ***mammalian CD69***, preferably human CD69 protein. Accordingly, the term 'human CD69' refers to a polypeptide which ***has or is homologous to (e.g., at least about 85%***...an amino acid sequence (SEQ ID NO:2)...or which is encoded by....a nucleic acids sequence ***homologous to (e.g., at least about 85%, 90%, 95% identical to) the naturally occurring human CD69***...or...a nucleic acid sequence that ***hybridizes to one of the foregoing nucleic acid sequences under stringent conditions***.... A preferred CD69 is a ***naturally occurring variant or allele*** of CD69." (see instant specification pages 45-46).

Therefore, the instant claims, given their broadest reasonable interpretation consistent with the instant specification, read on methods involving the administration of antibodies that bind everything ***from*** SEQ ID NO: 2 ***to a protein encoded by a nucleic acid sequence that hybridizes to a nucleotide sequence that is itself "degenerate to" or 85% identical to a "naturally occurring human CD69".***

Furthermore, in order to be ***useful*** for the claimed method, the anti-CD69 antibodies must recognize ***naturally occurring CD69***.

However, there is ***insufficient nexus*** between antibodies which bind ***a protein encoded by a nucleic acid sequence that hybridizes to a nucleotide sequence that is itself "degenerate to" or 85% identical to a "naturally occurring human CD69"*** **AND** antibodies which bind ***"naturally occurring CD69"***.

More particularly, the instant specification does not provide sufficient direction or guidance for the skilled artisan to know which particular ***variants of "naturally occurring human CD69" encompassed by the instant claims, such as proteins encoded by a nucleic acid sequence that hybridizes to a nucleotide sequence that is itself "degenerate to" or 85% identical to a "naturally occurring human CD69"***, will generate antibodies that, while able to bind the variant polypeptide, are **unable** to bind naturally occurring CD69, as required to be useful for the claimed method.

For example, even "naturally occurring" alleles of CD69 could be differentially recognized by the same antibody as shown for CD4 by Lederman et al. (Molecular Immunology 28: 1171-1181, 1991). Lederman describes that while human CD4 is relatively non-polymorphic protein, a single amino acid substitution present in a common CD4 allele can ablate binding of an anti-CD4 monoclonal antibody (see entire document).

Moreover, one of ordinary skill in the art would ***not*** be able to predict which particular amino acid changes in a variant of naturally occurring CD69 will not affect the ability of an antibody generated against the mutant protein to recognize the naturally occurring form.

For example, as illustrated by Colman et al. (Research in Immunology, 1994; 145(1): 33-36) even single amino acid changes in an antigen can effectively abolish antibody-antigen binding (see entire document, particularly page 34). Moreover, Abaza et al. (Journal of Protein Chemistry, Vol. 11, No. 5, 1992, pages 433-444) teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding (see entire document, particularly Results on pages 435-436).

Thus, the instant claims encompass in their breadth making antibodies to a multitude of polypeptides for which it is difficult to predict which mutation(s) will result in an antigen that will generate an antibody that will, in turn, bind a different protein, i.e., "naturally occurring CD69". Without sufficient guidance or direction for which amino acid sequences and which mutation(s) can be tolerated in the structures of these protein, while still retaining the structure necessary to generate an antibody that will recognized "naturally occurring CD69", the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicant is invited to claim the antibody with reference to the particular sequence that it recognizes, e.g., "wherein said depletor is a depleting antibody that binds SEQ ID NO: 2".

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. **Claims 56-60, 67-69 and 105-108 are rejected under 35 U.S.C. 103(a)** as being unpatentable over McInnes et al. (Immunol Today. 1998 Feb;19(2):75-9) in view of Ledbetter et al. (US 2003/0118592) and McInnes et al. #2 (Nat Med. 1997 Feb;3(2):189-95)(see entire documents).

Claims 58-60 recite a method comprising administering a "depleting anti-CD69 antibody".

It is noted that while the other claims under examination generically recite "early activation molecule depletor" or "CD69 depletor" be administered, ***as stated in the Restriction Requirement of October 11, 2006***, these claims have been ***restricted to the extent that they read on the administration of a "depleting anti-CD69 antibody" and will be examined as such, irregardless of the format of the claims.***

Therefore, claims 56, 57, 67-69 and 105-108 are also included in the instant rejection.

McInnes teaches that IL-15 mediates the recruitment and activation of T cells from the peripheral blood in rheumatoid arthritis patients. McInnes further teaches that IL-15 activation of T cells from rheumatoid arthritis patients rapidly upregulates CD69 expression, and that these $CD69^+$ T cells produce TNF-α and induce TNF-α production in macrophage. McInnes concludes that because IL-15 mediates T cell recruitment and activation in the synovial membrane, IL-15 is a novel target for neutralization with biological agents (see entire document, in particular page 76, box 1 and right column, 1st paragraph, Figure 2, and page 78, right column, "Therapeutic Implications").

McInnes does not teach using a depleting anti-CD69 antibody or a radiolabeled/toxin conjugated depleting anti-CD69 antibody to treat rheumatoid arthritis.

Ledbetter teaches human and humanized anti-CD69 antibodies with enhanced antibody dependent cell cytotoxicity and complement fixation activity, both of which lead to effective depletion of immune cells, such as B cells and T cells (see entire document, in particular pages 4-5, paragraphs [0021]-[0029], page 14, paragraph [0105] and claims 17 and 35). Ledbetter further teaches that radiolabeled antibodies and toxin conjugated antibodies are effective for treating tumors, such as B cell tumors (see in particular, pages 2-4, paragraphs [0011]-[0019]).

As would be well known to one of ordinary skill in the art, radiolabeled antibodies and toxin conjugated antibodies deplete the cells to which they bind by killing them.

Ledbetter also teaches that autoreactive T and B cells are present in rheumatoid arthritis patients (see in particular, pages 21-22 paragraph [0140]). Ledbetter claims that various depleting antibodies, including anti-CD69 antibody, can be used to treat various autoimmune diseases and tumors, including rheumatoid arthritis (see in particular, claims 1, 27, 35 and 57-60).

McInnes #2 teaches that ***anti-CD69 antibody blocks IL-15 activated T cell production/induction of TNFα*** in macrophage/monocytes (see entire document, in particular page 192, right coulumn, 1st paragraph and Discussion, pages 192-194).

Given the teachings of McInnes, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made that an excellent alternative to treating rheumatoid arthritis by neutralizing IL-15 would have been to treat rheumatoid arthritis by depleting CD69 expressing T cells with the depleting anti-CD69 antibody taught by Ledbetter.

One of ordinary skill would have been motivated to use the depleting anti-CD69 antibody of Ledbetter to treat rheumatoid arthritis because Ledbetter teaches that T cells are involved in rheumatoid arthritis and because McInnes teaches that CD69 expressing T cells are localized to the synovium of rheumatoid arthritis patients where they produce TNFα, a well known rheumatoid arthritis disease mediator, as taught by McInnes.

One of one of ordinary skill in the art would have been further motivated to use the depleting anti-CD69 antibody of Ledbetter to treat rheumatoid arthritis because such an antibody would be doubly effective in treating rheumatoid arthritis in that it would not only deplete $CD69^+$ T cells, but also for those CD69 T cells that are bound by the anti-CD69 antibody but resist depletion, the anti-CD69 antibody would, at the very least, prevent CD69 expressing T cells from inducing TNFα production in macrophage, as taught by McInnes #2 .

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Accordingly, the instant claims are unpatentable over McInnes in view of Ledbetter and McInnes et al. #2.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Patent Examiner
January 22, 2007

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